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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/898,556 | 07/03/2001 | C. Frank Bennett | RTS-0248 | 2718 |

7590 05/29/2002

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| EXAMINER | |
|---|---|
| LACOURCIERE, KAREN A | |
| ART UNIT | PAPER NUMBER |
| 1635 | 10 |

DATE MAILED: 05/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/898,556 | Applicant(s) BENNETT ET AL. | |
|---|---|---|---|
| | Examiner Karen Lacourciere | Art Unit 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☒ Interview Summary (PTO-413) Paper No(s). 9 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Applicant should note, the computer readable form of the sequence listing has been corrected to delete non-ASCII "garbage" at the beginning or end of the file. No action is required on the part of Applicant in regards to the sequence listing.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-10 and 12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "said nucleic acid molecule encoding HRK1" in lines 3 to 4 of the claim. There is insufficient antecedent basis for this limitation in the claim, because the preceding lines in the claim are directed to a nucleic acid encoding HKR1. Claims 2, 4-10 and 12-20 are indefinite for the same reasons due to dependence on claim 1.

Claim 1 is indefinite because it recites the limitation "HRK1" (in two places in line 4). One of ordinary skill in the art would not know what the compound of claim 1 inhibits because the specification has not defined the term "HRK1". Claims 2, 4-10 and 12-20 are indefinite for the same reasons due to their dependence on claim 1.

The reference to "HRK1" in claim 1 appears to be due to a typing error, as the instant specification is directed to compounds that hybridize to and inhibit the expression of HKR1. In the search and examination of the instant case, claim 1 and dependent claims have been considered to be drawn to compounds that specifically hybridize with a nucleic acid encoding HKR1 and inhibit the expression of HKR1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* (cell culture) inhibition of HKR1, does not reasonably provide enablement for *in vivo* (whole organism) methods of treatment using antisense targeted to HKR1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 15-20 are drawn broadly to inhibition of the expression of HKR1 in any cell *in vivo* (whole organism) for the treatment of any disease that is associated with HKR1. Claims 17-20 are further drawn to treating any hyperproliferative disorder, including lung, brain and breast cancer, using antisense targeted to a nucleic acid encoding HKR1.

The specification provides examples wherein chimeric phosphorothioate antisense targeted to a nucleic acid encoding HKR1 inhibited the expression HKR1 *in vitro* (cell culture) in human cell lines. The specification does not demonstrate any correlation with the inhibition of HKR1 in cells in culture and a treatment effect for any disease or condition associated with HKR1. The specification does not present any examples wherein antisense targeted to HKR1 was delivered to cells *in vivo* (whole organism), nor wherein antisense targeted to HKR1 inhibited the expression of HKR1 in cells *in vivo* (whole organism). The specification does not provide any examples wherein treatment effects were obtained for any disease or condition, including a hyperproliferative disorder, including lung, brain or breast cancer, using antisense targeted to HKR1.

The specification does not present any guidance on what specific diseases or conditions can be treated using antisense targeted to HKR1, including specific hyperproliferative disorders, and what cells to target for a particular disease or condition. The claims include methods directed to treating certain types of cancers, lung, brain and breast, however, these types of cancer would encompass a variety of specific cancers and the specification has not provided any guidance on what specific

lung, brain or breast cancers would respond to treatment using antisense targeted to HKR1.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been

established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein antisense is delivered to cells *in vitro* and the expression of HKR1 is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a

concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to HKR1 to generally any target cell or tissue *in vivo* (whole organism) at a concentration effective to provide a pharmaceutical effect or to treat the broad range of diseases encompassed by the claims.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific diseases and conditions can be treated by the inhibition of the expression of HKR1, what specific cells to target with HKR1 antisense for the treatment of a particular disease or condition, and how to specifically deliver antisense to a target cell *in vivo* (whole organism) at a concentration effective to result in inhibition of the expression of HKR1 to a level sufficient to result in a pharmaceutical effect or to treat a disease. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo*. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods of treatment claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of treatment using antisense, the lack of specific guidance for the *in vivo* (whole

organism) application of antisense methods of treatment and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods of claims 15-20 over the full scope claimed without undue trial and error experimentation.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2 and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oguri et al. (reference AF on PTO form 1449, filed 07-03-01) in view of Taylor et al.

(DDT, Vol. 4, No. 12, Dec. 1999), Milner et al. (Nature Biotechnology, Vol. 15, June 1997), and Baracchini et al. (US Patent No. 5,801,154).

Oguri et al. teach the full length sequence of a nucleic acid encoding HKR1, SEQ ID NO: 3 (see figure 1 of Oguri et al.). Oguri et al. teach that HKR1 (SEQ ID NO: 3) expression is induced by platinum drugs in human lung adenocarcinoma cells, both *in vitro* and *in vivo*, but that the "functions of the HKR1 remain to be elucidated" (see page 66, first paragraph) and the role of HKR1 in platinum drug resistance or metabolism is uncertain. Oguri et al. teach, "Further studies are required to clarify the association between HKR1 mRNA overexpression and platinum drug resistance and/or metabolism". Oguri et al. do not teach antisense targeted to HKR1 mRNA, nor do they teach the modifications to antisense claimed.

Taylor et al. teach antisense as a research tool to elucidate the function of any gene of known sequence.

Milner et al. teach methods of making and screening antisense molecules against a desired target gene in any region of the gene, including the 5' or 3' untranslated regions or the coding region.

Baracchini et al. teach 2'-O-methoxyethyl sugar modifications, 5-methyl cytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity and teach antisense oligonucleotides of 8-30 nucleotides in length (see for example columns 6-9). Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to make an antisense molecule targeted to a nucleic acid encoding HKR1 (SEQ ID NO:3), based on the sequence taught by Oguri et al., because methods of making antisense targeted to a known gene were well known in the art, as exemplified by Milner et al. The art recognized antisense as a research tool, useful for clarifying the role of a gene, and Oguri et al. identified HKR1 as a target gene whose function was not well defined (see page 66, first paragraph, for example) and merited additional study because of its association with lung cancer cell response to platinum chemotherapy both *in vivo* and *in vitro* (see for example, p 66, third paragraph). It further would have been obvious to make such antisense of a length within the range of 8-50 nucleobases (as taught by Baracchini et al.), because antisense of a short length are more easily synthesized and easier to deliver to cells, and this size range was conventional in the art. It would have been further obvious to make said antisense comprising modifications, including 2'-O-methoxyethyl, 5-methyl cytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, as taught by Baracchini et al., because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule (see for example Baracchini et al. column 6, paragraph 3). It would have been obvious to one of ordinary skill in the art to make a composition comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with

antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al.

One of ordinary skill in the art would have been motivated to make antisense targeted to HKR1 (SEQ ID NO: 3), because antisense was well known in the art as a means to selectively inhibit the expression of a gene and can be designed with minimal information (i.e. nucleotide sequence)(see for example Taylor, p 564, second column). One of ordinary skill in the art would have been motivated to make antisense to HKR1 (SEQ ID NO: 3) to use *in vitro* in order to determine the role of HKR1 in the response to platinum therapeutics, because antisense would have selectively inhibited HKR1 and because the art did not provide any other type of inhibitor for HKR1, or enough information about HKR1 to design any other type of inhibitor. One of ordinary skill in the art would have been motivated to make such antisense 8-50 nucleotides in length and with the modifications and in the compositions taught by Baracchini et al. for the benefit of ease of delivery and synthesis, and to realize the benefits of improved stability and hybridization properties these modifications provided.

One skilled in the art would have expected to be able to find antisense which inhibits the expression of HKR1, because the sequence of a nucleic acid encoding HKR1 (SEQ ID NO: 3) was known in the art and antisense could "be designed to inhibit any gene target provided that the sequence is known" (Taylor et al., p 562, column 1, second paragraph), methods of screening for antisense to a known gene was routine (see for example Milner et al.).

It would have been obvious to one of ordinary skill in the art to use antisense targeted to a nucleic acid encoding HKR1 in a method of inhibiting the expression of HKR1 (SEQ ID NO: 3) in cells *in vitro* (cell culture), because it would be an obvious use for an antisense molecule designed to hybridize to and inhibit the expression of a nucleic acid encoding HKR1. One of ordinary skill in the art would have been motivated to use antisense targeted to a nucleic acid encoding HKR1 (SEQ ID NO: 3) to inhibit the expression of HKR1 in cells *in vitro* because the upregulation of HKR1 expression in cells treated with platinum *in vitro* was demonstrated to correlate with upregulation in cells treated with platinum *in vivo* and would have provided a model to study the role of HKR1 in cellular response to platinum.

Therefore, at the time the instant invention was made, the invention of claims 1, 2 and 4-15, as a whole, would have been obvious to one of ordinary skill in the art.

## ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere PATENT EXAMINER TC1600
May 24, 2002